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| EXAMINER | |
|---|---|
| HA, JULIE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/579,641 | NELSON ET AL. | |
| | Examiner | Art Unit | |
| | JULIE HA | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-32* is/are pending in the application.

4a) Of the above claim(s) *14-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Amendment after Non-final office action filed on May 11, 2009 is acknowledged. Claim 2 has been cancelled. Claims 1 and 3-32 are pending in this application. Applicant elected Group I in the reply filed on July 16, 2008. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)). The restriction requirement was deemed proper and made FINAL in the previous office action. Claims 14-32 remain withdrawn from further consideration, as being drawn to nonelected inventions. Claims 1 and 3-13 are examined on the merits in this office action.

### *Withdrawn Objection and Rejections*

1. The objection to specification due to grammatical errors is hereby withdrawn in view of Applicant's amendment to the specification.

2. The objection to the specification in regards to page 8 of specification is hereby withdrawn in view of Applicant's amendment to the specification.

3. The objection to the specification in regards to page 9 of specification is hereby withdrawn in view of Applicant’s amendment to the specification.

4. Claims 1, 3 and 5-13 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with enablement requirement is hereby withdrawn in view of Applicant's amendment and arguments.

5. Claims 1, 8-11 and 13 rejected under 35 U.S.C. 102(b) as being anticipated by Hu et al (Molecular Cell, April 2002, 9: 789-298, filed with IDS) is hereby withdrawn in view of Applicant's amendment to the claims.

6. Claims 1 and 5-13 rejected under 35 U.S.C. 102(b) as being anticipated by Hamilton et al (US 2002/0146701 A1) is hereby withdrawn in view of Applicant's amendment to the claims.

***Maintained and Revised Rejections***

***35 U.S.C. 112, 2nd***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 3-13 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. The base claim 1 recites, "A protein interaction system comprising…a first fluorogenic fragment of fluorogenic fragment of fluorescent protein wherein the fragment is provided by splitting the fluorescent protein at a site(s) to form complementary fragment such that when complementary fragments of the fluorescent protein are functionally associated with each other, a fluorescent signal capable of being detected is generated…" It is unclear what modifications are included in "functionally associated with each other". For example, it is unclear what is required to have the first fluorogenic

fragment of fluorescent protein to functionally associate with the complementary fragment of the fluorescent protein. Because claims 3-13 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

***Response to Applicant's Arguments***

10. Applicant argues that "the mechanism by which complementary fragments of a fluorogenic fragments of a fluorescent protein can generate a fluorescent signal when fused to proteins that interact with each other is referred to at page 4, lines 22 too 28 of the specification, and is further described in the cited prior art document of Hu et al, wherein the process is referred to as 'biomolecular fluorescence complementation (BiFC)'".

11. Applicant's arguments have been fully considered but have not been found persuasive. Page 4, lines 22 to 28 of the specification describes that "fluorescence can be generated following the functional association of two separate fragments of the GFP molecule (hapto-GFPs) when driven by the interaction of a pair of proteins fused via a linker to the new C' and N' termini of the hapto-GFPs." This paragraph does not describe what type of association is required to form a "functional association". Hu reference does not define what type of interaction or association is required for a "functional association" to occur. Therefore, it is unclear what is required to have the first fluorogenic fragment of fluorescent protein to functionally associate with the complementary fragment of fluorescent protein. The dictionary defines associate as "to join or connect together" (see http://www.merriam-webster.com/dictionary/associate).

Therefore, it is unclear what is required for the protein to functionally associate with the complementary fragment.

### *35 U.S.C. 112, 1st*

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 3, 5-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court

determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a protein interaction system comprising a plurality of bait fusion protein, each fusion protein comprising: a first fluorogenic fragment of fluorescent protein wherein the fragment is provided by splitting the fluorescent protein at a site(s) to form complementary fragments such that when complementary fragments of the fluorescent protein are functionally associated with each other, a fluorescent signal capable of being detected is generated, a first peptide of interest wherein the first peptide of interest of each bait fusion protein is identical to the first peptide of interest in each of the other bait fusion proteins, and a linker portion interposed between the first peptide and first fluorogenic fragment; wherein the linker portions of each bait fusion protein are of different lengths comprising multiples of the pentapeptide sequence GGGGS, and the first peptide of interest of each bait fusion protein is identical to the first peptide of interest in each of the other bait fusion proteins, and at least one prey fusion protein comprising a fluorogenic fragment of the fluorescent protein complementary to said first fluorogenic fragment of fluorescent protein, a second peptide of interest, and a second linker portion (GGGGS) interposed between the complementary fluorogenic fragment and the second peptide; wherein on interaction of a first peptide of interest with a second peptide of interest, the fluorogenic fragments of the fluorescent protein functionally associate to promote fluorescence. The generic statements bait fusion proteins, fluorogenic fragment of fluorescent protein, a first peptide of interest, prey fusion protein, and a second peptide of interest do not provide

ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide or amide bonds, and make up the class of proteins, linkers and fluorescent protein. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules, and other synthetic peptide or peptide-like molecule that can form peptide bonds, and function as proteins, linkers and fluorescent proteins.

The specification discloses that fluorescence will only be promoted when peptides of interest of bait and prey fusion proteins, having suitable linker lengths to allow the respective fluorescent protein fragments to associate are used (see paragraph [0021] of instant specification US 2007/0111192 A1). The specification discloses that the provision of a peptide or interest linked to a fluorescent fragment via a range of linker lengths is advantageous over a single linker length as such a range maximizes the chances of an interaction between peptides of interest being detected and minimizes the chances that the fluorescent fragments cannot associate with each other due to stereochemical hindrance or that the linkers are too flexible (see paragraph [0022] of instant specification as described above). The specification discloses that the linker portions comprise in the range 5 to 60 amino acid residues, more preferably in the range 20 to 60 amino acid residues...at least 20 amino acids (see paragraphs [0027]-[0028] of instant specification as described above). The specification is limited to the linker sequence GGGGS (SEQ ID NO:1) (see paragraph [0033] of instant specification as described above) and multiples of a pentapeptide sequence GGGGS. The specification discloses that such sequences provide advantageous flexibility properties and thus enable the linker region to be readily extended to provide a robust screening method (see paragraph [0056] of instant specification as described above).

The specification discloses that the fluorescent protein is any fluorescent protein in which appropriate split sites can be formed and which the resulting fragments can associate with each other and cause fluorescence may be used...Examples of fluorescent protein include RFP, BFP, YFP, CFP, and variants of GFP (see paragraph

[0034] of instant specification described above). The specification discloses that the fragments of fluorescent protein (fluorogenic fragments) are generatable through the introduction of a split point between the amino acids at positions 157 and 158, or between the amino acids at positions 172 and 173 of the humanized form of GFP (SEQ ID NO:2) (see paragraph [0037] of instant specification as described above). Further, the specification discloses that alternate split points are between residues 23/24, 38/39, 50/51, 76/77, 89/90, 102/103, 116/117, 132/133, 142/143, 190/191, 211/212 or 214/215 of EGFP (see paragraph [0040] of instant specification as described above).

The specification discloses that the peptides of interest linked to the fragments of fluorescent protein can be small peptides of differing amino acid sequence, for example nonomers, comprising different amino acid compositions or the same over composition, but with the amino acid present in a different order. Alternatively, the peptides may be full size proteins, e.g. obtained from a cDNA library. Peptides may be produced synthetically or recombinantly using techniques which are widely available in the art. For peptides translated in the cell, naturally or induced, post-translational modification for example glycosylation, lipidation, phosphorylation of the peptides may occur, and these post translated products are still to be regarded as peptides (see paragraph [0048] of instant specification described above).

The working example 1 describes generation of GFP fragments (see paragraphs [0138]-[0142] of instant specification as described above). Example 2 describes the effect of varying the length of the intervening hydrophilic linkers interposed between complementary fragments of fluorescent protein and leucine zipper proteins known to

bind to each other (see Example 2). The specification discloses that "in order to ascertain that the haptoEGFP tagged glycoproteins were capable of forming a biologically active complex at the cell membrane cells were transfected with constructs expressing a number of different H and F chimeras…By three days post-transfection, cell to cell fusion was detected over large areas of the monolayer" (see Example 4). The specification does not describe any other bait fusion protein, prey protein, linkers, fluorogenic fragment and fluorescent protein, such as any other type of peptide or peptide-like molecule, small organic molecules, peptidomimetics, amino acid mimetics that act as peptides, proteins, linkers, fluorogenic fragment and fluorescent proteins. Description of a pentapeptide linker GGGGS and EGFP fluorescent protein, and fragments of EGFP is not sufficient to encompass numerous other fragments of other fluorescent proteins, bait fusion proteins and prey proteins that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, there are infinite numbers of possible bait fusion and prey proteins, since the only description of these proteins are of their functions. Again, the different possibilities depend on the number of amino acids. Thus, if the bait fusion protein contained 100 amino acid residues, then there are $100^{20} = 1 \times 10^{40}$ different possibilities. Therefore, the number of possible bait fusion proteins and prey proteins are vast. Furthermore, the split points described in the specification is for EGFP only, and not for all other fluorescent proteins. Additionally, the specification does not describe the kind or size of different proteins from the myriad of known proteins the ones that can be fused to GFP without destroying the function of

GFP. The claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention. Therefore, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

***Response to Applicant's Arguments***

14. Applicant argues that "the description requirement is more easily met if a recited genus consists of compounds known in the art, e.g., fluorescent proteins, as opposed to a recited genus of hypothetical compounds." Applicant argues that "where a genus is already known in the art, the genus may be adequately described without providing detailed structures of a representative number of compounds within the genus." Applicant argues that "fluorescent proteins are a well-characterized genus of molecules…the expression 'fluorogenic fragment of fluorescent protein' is likewise

supported by the written description of the specification, given the knowledge of the art. The expression encompasses a fragment of a fluorescent protein embracing the structural feature that the fragment may functionally associate with a complimentary fragment to generate a fluorescent signal. A person skilled in the art would be aware that fluorescent proteins may be cleaved to form two fragments, which may functionally associate with each other when brought together in the appropriate orientation to form a species capable of generating a fluorescent signal." Applicant argues that "approximately 14 potential split points in EGFP are described giving rise to fluorescent fragments."

Applicant argues that "in relation to the terms 'a first peptide of interest' and 'a second peptide of interest', it is submitted that the nature of the invention would not allow a restriction of these terms by a further structural definition…it is clear from the teaching on page 13 of the specification that a peptide of interest may be a small peptide or a full size protein, and these may be provided in different ways…is provided a screening method that may be used to determine whether and/or how the first peptide of interest and the second peptide of interest interact. In this embodiment, the invention does not require prior knowledge of the possible interaction of the peptides of interest, let alone knowledge of the amino acid sequence or structure of the peptides of interest." Applicant further argues that "in one embodiment of the invention, linkers of suitable length and character are provided, as defined in the amended claim, such that, in contrast to the prior art, any proteins may be selected as bait and prey peptides of interest as they will not prevent the binding of fluorogenic fragments."

15. Applicant's arguments have been fully considered but have not been found persuasive. The mere fact that the fluorescent proteins, peptides and proteins are known in the art has no bearing on the claims. The MPEP states the following: For the written description requirement, an Applicant's specification must reasonably convey to those skilled in the art that the applicant was in possession of the claimed invention as of the date of the invention. *Reagents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67, 43 USPQ 2d 1398, 1404-05 (Fed. Cir. 1997)" (see MPEP 2106 V 1). The basis of the written description rejection is based on 1) the structure and function and 2) representative number of species (see MPEP 2105 ). As described above, "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398. The MPEP states that "…adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., Eli Lilly. Description of a representative number of species does not require the

description to be of such specificity that it would provide individual support for each species that the genus embraces" (see MPEP 2163).

The claims only recite functional characteristics. The claims do not define or recite any structural correlation to the functional characteristics. The claims do not define what structural features are required to have the functional characteristics as a bait protein, prey protein, and what fragments are required to "functionally associate" with each other. The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618. As indicated above, description of a pentapeptide linker GGGGS and EGFP fluorescent protein, and fragments of EGFP is not sufficient to encompass numerous other fragments of other fluorescent proteins, bait fusion proteins and prey proteins that

belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, there are infinite numbers of possible bait fusion and prey proteins, since the only description of these proteins are of their functions. Again, the different possibilities depend on the number of amino acids. Thus, if the bait fusion protein contained 100 amino acid residues, then there are $100^{20} = 1 \times 10^{40}$ different possibilities. Therefore, the number of possible bait fusion proteins and prey proteins are vast. Furthermore, the split points described in the specification is for EGFP only, and not for all other fluorescent proteins. Additionally, the specification does not describe the kind or size of different proteins from the myriad of known proteins the ones that can be fused to GFP without destroying the function of GFP. The claims do not describe a single structural feature. Knowing the linker sequence still does not define the structural correlation between structure and function of the peptides or proteins. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention. Therefore, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed. The numbers of possible peptides and proteins are vast and therefore the number of bait fusion protein comprising a first fluorogenic fragment and a complementary fragment of fluorescent protein fused to a prey fusion protein are vast, as described above.

In regards to Applicant's argument that "in relation to the terms 'a first peptide of interest' and 'a second peptide of interest', it is submitted that the nature of the invention would not allow a restriction of these terms by a further structural definition…it is clear

from the teaching on page 13 of the specification that a peptide of interest may be a small peptide or a full size protein, and these may be provided in different ways…is provided a screening method that may be used to determine whether and/or how the first peptide of interest and the second peptide of interest interact. In this embodiment, the invention does not require prior knowledge of the possible interaction of the peptides of interest, let alone knowledge of the amino acid sequence or structure of the peptides of interest." Again, the claims are only defined in functional characteristics. As MPEP stated above, “if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.” Even though the screening methods are known and provided in the specification, this still does not provide any correlation between function and structure of the sequence of prey and bait fusion proteins.

In regards to Applicant’s argument that “approximately 14 potential split points in EGFP are described giving rise to fluorescent fragments.” As described below, Hamilton et al (US 2002/0146701 A1) teach that inserts of short sequence LEEFGS between adjacent residues at 10 internal insertion sites were tried. Of these, inserts at three sites, between residues 157-158, 172-173 and 194-195 gave fluorescence of at least 1% of that of wild type GFP. Only inserts between residues 157-158 and 172-173 had fluorescence of at least 10% of wild type GFP (see paragraph [0008]). The split points described in the specification is for EGFP only, and not for all other fluorescent proteins. Other variants of GFP, such as blue fluorescent protein, yellow fluorescent protein may

have different split points, and may have small amounts of fluorescence compared to the wild type or EGFP. Please note that the Hamilton reference was used to rebut Applicant's argument.

The *In re Wilder* reference was to describe that "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention". (See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984)). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention. Therefore, the rejection is maintained.

***35 U.S.C. 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1 and 3-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al in view of Hamilton et al (US 2002/0146701 A1) as evidenced by http://www.biovision.com/updated/egfp.html in view of Michnick et al (US 2004/0161787 A1, claims benefit to provisional application No. 60/445,225, filed on Feb. 6, 2003).

20. Hu et al teach a composition comprising proteins fused to different fragments of yellow fluorescent proteins (YFP) connected by linker peptides of different lengths (for example, KQKVMNH and RSIAT) (see p. 797, left column, “Experimental Procedures”). The reference further teaches a protein of interest and two different linkers interposed between the YFP and the protein of interest (see page 797, left hand column). The reference teaches that green fluorescent proteins forms through an autocatalytic cyclization reaction subsequent to protein folding (see p. 790, left column, 2nd paragraph). The Experimental section teaches that bZIP domains and EYGP fragments (enhanced Yellow fluorescent protein) were connected by linker peptides (KQKVMNH

and RSIAT) and were fused to amino-terminal hexahistidine purification tags. The fusion proteins were expressed in E. coli and purified using nickel chelate affinity chromatography (see p. 797, left column, first full paragraph). Further, the reference teaches that hexahistidine-tagged proteins containing the bZIP domains of Jun and Fos fused to the N- and C-terminal EYFP fragments as well as bZIP Jun fused to full-length EYFP (see p. 797, left column, 3rd full paragraph). The difference between the reference and the instant claims is that the reference does not teach EGFP and the split sites of 157/158 and172/173, plurality of prey fusion proteins, and prey fusion proteins having different amino acid sequences and linker having multiples of the pentapeptide sequence glycyl-glycyl-glycyl-glycyl-serine.

21. However, Hamilton et al teach a method of reconstituting, folding, or reassembling peptides or other binding pairs into a functionally active protein or other complexes using an antiparallel leucine zipper. The reference teaches assays using fusion proteins comprising GFP fragment and test polypeptides for investigating protein-protein interactions (see abstract). The reference teaches a pair of helices, NZ and CZ capable of forming an antiparallel leucine zipper designed to fuse to the dissected GFP fragments via linkers to form NZGFP (N-terminal GFP) and CZGFP (C-terminal) (see paragraph [0061]). The reference claims a protein complex comprising a first and second peptide, each of said peptides being joined to a heterogonous helical domain, said helical domains being noncovalently associated to form an antiparallel leucine zipper, wherein said peptides form a signaling moiety while complexed, wherein said first and second peptides are joined to said helical domains via a linker, wherein each of

the first and second peptides comprises a distinct portion of green fluorescent protein (GFP) (see claims 1-4). The reference teaches that inserts of short sequence LEEFGS between adjacent residues at 10 internal insertion sites were tried. Of these, inserts at three sites, between residues 157-158, 172-173 and 194-195 gave fluorescence of at least 1% of that of wild type GFP. Only inserts between residues 157-158 and 172-173 had fluorescence of at least 10% of wild type GFP (see paragraph [0008]). Hamilton teaches that GFP mutants with improved solubility properties at higher temperatures and are able to fluoresce at 37ºC…a GFP mutant in which phenylalanine is replaced by a leucine (see paragraph [0058]). As evidenced by http://www.biovision.com/updated/egfp.html, any enhanced fluorescent protein gives off a better signal (fluorescence).

22. Furthermore Michnick et al teach that protein fragment complementation assays for drug discovery (see abstract). The reference teaches assays using GFP for PCA. The reference teaches a flexible 10-amino acid linker consisting of $(GGGGS)_2$ (SEQ ID NO:1) separated the genes of interest and the YFP fragments. The reference teaches that the use of a flexible linker between the gene of interest and the reporter fragment assures that the orientation and arrangement of the fusion is optimal to bring the protein fragments into close proximity. GFP[1] corresponds to amino acids 1 to 158 and GFP [2] corresponds to amino acids 159 to 239 of GFP (see paragraph [0153]).

23. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of the references, since the reference teach the protein interaction system utilizing fluorescent protein fragments and different proteins.

Michnick teaches the flexible linker consisting of GGGGSGGGGS. One of ordinary skill in the art would have been motivated to combine the teachings, since Hu teaches both GFP and EYFP fragments and linkers of sizes 5 and 7 for protein interaction system, and Hamilton teaches GFP at split points 157-158, 172-173 and 194-195, 4-6 amino acid residue linker and different proteins for protein interaction system, and Michnick et al teach the GFP complementation assays utilizing flexible linker GGGGSGGGGS separating the genes of interest and the YFP fragments. Furthermore, Michnick et al teach that a flexible linker between the gene of interest and the reporter fragment assures that the orientation and arrangement of the fusion is optimal to bring the protein fragments into close proximity. Furthermore, it would have been obvious to try using enhanced green fluorescent protein, since it gives off a better signal and as indicated by Hamilton, certain GFP mutants had improved solubility properties and are able to fluoresce at 37ºC. Furthermore, it would have been obvious to one of ordinary skill in the art to try different linker lengths for optimal lengths for the fluorescent fragments to reassociate with each other to generate fluorescent signal. Additionally, as taught by Michnick et al, flexible linkers assures that the orientation and arrangement of the fusion is optimal to bring the protein fragments into close proximity. One of ordinary skill in the art would have been motivated to try EGFP, since Hu teaches the protein interaction system utilizing EYFP. The MPEP states the following in regards to range: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are*

*disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). There is a reasonable expectation of success, since bZIP proteins and EYFP (fluorescent protein) fragments and heterologous protein interaction systems have been successful, and the use of GFP with bZIP was successful, thus one would at least expect that EGFP would at least have the same effect. Therefore, the different linker lengths and different numbers of prey proteins and amino acid sequences of prey proteins are deemed

merely a matter of judicious selection and routine optimization that is well within the purview of skilled artisan.

***Response to Applicant's Arguments***

24. Applicant argues that Hu et al nor Hamilton et al disclose linker portions interposed between the first peptide and first fluorogenic fragment wherein the linker portions of each bait fusion protein are of different lengths comprising multiples of a pentapeptide sequence GGGGS...Neither Hu nor Hamilton provide any indication that such linker portions would be advantageous or would maximize the chances of an interaction between peptides of interest being detected."

25. Applicant's arguments have been fully considered but have not been found persuasive. However, Michnick et al teach protein fragment complementation assays for drug discovery (see abstract). The reference teaches assays using GFP and the use of a flexible 10-amino acid linker consisting of $(GGGGS)_2$ (SEQ ID NO:1) separated the genes of interest and the YFP fragments. The reference teaches that the use of a flexible linker between the gene of interest and the reporter fragment assures that the orientation and arrangement of the fusion is optimal to bring the protein fragments into close proximity. Therefore, the Michnick reference gives motivation to use the flexible linker for fluorescent protein fused to the protein of interest. Therefore, the combined arts are *prima facie* obvious over the instant claims 1 and 3-13.

### *New Objection*

26. Claims 1 and 12 are objected to for the following reasons: Claims 1 and 12 recite an amino acid sequence glycyl-glycyl-glycyl-glycyl-serine. The peptide sequence is missing the sequence identifier. The proper way to claim a peptide sequence is for example, GGGGS (SEQ ID NO:1) (see 37 CFR 1.821(d)). This error should be corrected.

### *Conclusion*

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654